PULMONARY REGURGITATION IN CONGENITAL HEART DISEASE

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The most important and best described clinical context for pulmonary regurgitation occurs in patients with repaired Tetralogy of Fallot. The first section deals briefly with pulmonary regurgitation in other situations; the remainder of the article deals with tetralogy of Fallot.

PULMONARY REGURGITATION IN CONDITIONS OTHER THAN TETRALOGY OF FALLOT

Isolated pulmonary regurgitation, in an otherwise normal heart, is well tolerated for decades. However, in a meta-analysis reported in the literature, 29% of patients had developed symptoms within 40 years.[1] Many patients with a right ventricle to pulmonary artery conduit develop a mixture of obstruction and regurgitation across the conduit. However, some of these patients have regurgitation as the dominant lesion, and feature in pulmonary valve replacement series.[2 3]

Even valvar pulmonary stenosis treated surgically or by balloon dilatation can lead to significant pulmonary regurgitation requiring valve replacement. Fifty-seven per cent of patients had moderate to severe pulmonary regurgitation in a balloon dilatation series,[w1] and in a surgical pulmonary valvotomy series 9% of patients required pulmonary valve replacement.[w2]

In pulmonary regurgitation secondary to pulmonary hypertension, the clinical picture is dominated by the primary lung disease or the high pulmonary vascular resistance rather than the volume load.

Severe acute pulmonary regurgitation driven by a large duct can occur in neonatal Ebstein's anomaly,[4] or following balloon dilation of critical pulmonary stenosis or perforation of valvar pulmonary atresia. If this torrential pulmonary regurgitation is accompanied by tricuspid regurgitation, a circular shunt may occur, due to right-to-left shunting across the atrial communication and left-to-right shunting at the duct resulting in poor systemic blood flow. Prostaglandins are stopped and in the most unstable patients, urgent duct ligation may be required. Attempts to decrease pulmonary regurgitation by pulmonary vasodilatation (increased ventilation, oxygen, nitric oxide) may be more successful if the tricuspid valve is competent.

PULMONARY REGURGITATION IN REPAIRED TETRALOGY OF FALLOT

Repair of tetralogy of Fallot is one of the success stories in the management of congenital heart disease. Yet many patients require multiple procedures, have limited exercise tolerance, develop arrhythmias and have a curtailed survival. Most of these problems relate to the state of the right ventricle late after repair, and its interaction with the pulmonary arterial tree and the left ventricle.

Early mortality was very high when complete repair of tetralogy was first attempted, but with experience and introduction of the two-stage repair hospital deaths decreased rapidly—for example, Kirklin reported a decline in early mortality from 50% in 1955 to 7% by 1964.[w3] Thus the earliest cohort of patients with repaired tetralogy are elite survivors and are likely to have the most favourable anatomy.[w4] In the early series of tetralogy of Fallot repair, much attention was focused on problems of residual obstruction (right ventricular outflow tract, pulmonary arterial stenoses) or residual ventricular septal defects which were major causes of early morbidity and mortality and the most frequent cause of reoperations.[w5–8] By the late 1970s exercise intolerance in the presence of a low pressure and dilated right ventricle was increasingly being recognised.[5 w9–12] Since then, evidence has continued to accumulate of the deleterious effect of chronic pulmonary regurgitation on the right ventricle. However, it must be emphasised that in most patients the manifestations of pulmonary regurgitation do not become apparent for decades.

The effects of more contemporary management protocols, with a trend towards early complete repair and high transannular patch rates, remain to be seen.

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PATHOPHYSIOLOGY OF PULMONARY REGURGITATION

Anatomical substrate and transannular patches

There is great variability in the dimensions of the tetralogy right ventricular outflow tract, main pulmonary artery and branch pulmonary arteries, both between patients and within the same patient.[6] Typically the infundibulum, pulmonary valve and main pulmonary artery are smaller in tetralogy patients than in normal individuals. The tetralogy right pulmonary artery/left pulmonary artery (RPA/LPA) dimensions were measured at 4–6 standardised locations, and their distributions overlapped considerably with controls. However, the tetralogy RPA/LPA dimension distributions were skewed to smaller values.[6]

Ehrenhaft was the first to demonstrate that a transannular patch could be avoided in most patients if a determined effort was made to resect and divide infundibular muscle, with only one transannular patch used in 70 consecutive repairs with a mortality of 19%, which was representative of the era.[7] Currently the highest transannular patching rates of approximately 80–85% have been reported by centres that perform complete repair in the first 1–3 months of life.[w13] [w14] A low transannular patching rate can be achieved for elective repair in early infancy if patients with the most favourable anatomy are chosen. Parry reported a small series (n = 42) of pink infants with tetralogy of Fallot repaired at 4–87 days (median 62 days), with 25% receiving transannular patches.[w15]

The real issue is the strategy for cyanotic tetralogy in the first 90–120 days. It is noteworthy that in the series of cyanotic tetralogy infants (n = 56) reported by Sousa Uva, those that underwent initial palliation (n = 15), despite having the most unfavourable anatomy, had a transannular patching rate of 13% when they ultimately underwent complete repair, whereas a transannular patch was used in 56% of patients that underwent primary repair at a median of 2.9 months.[w16] Growth of the junction of the right ventricle and pulmonary trunk and pulmonary arteries following a shunt is well described,[w17] although many years later acquired atresia may also occur.[w18] In Sousa Uva's cohort the right ventricle–pulmonary artery junction median Z score increased from −2.6 to 1.3 by the time of complete repair. Growth can also be achieved by balloon dilatation of the pulmonary valve and branch pulmonary arteries.[w19]

Although a transannular patch is unavoidable in some patients, even patients who undergo a pulmonary valvotomy can develop clinically significant pulmonary regurgitation. Indeed, patients with isolated valvar pulmonary stenosis that have had surgical or transcatheter relief of obstruction can also develop severe pulmonary regurgitation necessitating pulmonary valve replacement.[w20]

Haemodynamic determinants

Pulmonary regurgitation is driven by the diastolic pressure difference between the pulmonary artery and the right ventricle. These pressure differences are often small. Hence small increments in airway or intrathoracic pressure can increase pulmonary regurgitation notably. Increased pulmonary regurgitation caused by elevated intrathoracic pressure is relevant in the immediate postoperative period, particularly in ventilated patients who have acute restrictive right ventricular physiology.[8] [w21]

However, in the chronic phase the most important determinants are the right ventricular stiffness and right ventricular afterload. A stiff right ventricle will raise the right ventricular diastolic pressure and decrease the gradient for pulmonary regurgitation. The basis for changes in ventricular stiffness are poorly understood. However, ventricular stiffness is thought to increase with hypertrophy or increased fibrosis.[w22–24]

Evaluating right ventricular diastolic function is extremely difficult. A marker of a stiff right ventricle is the antegrade transmission of the atrial "A" wave into the main pulmonary artery, in all phases of respiration, with the stiff right ventricle in diastole acting as a passive conduit. This can either be demonstrated using pressure measurements (fig 1) or more commonly by pulse wave Doppler echocardiography (fig 2) or magnetic resonance imaging (MRI) flow measurements. Gatzoulis demonstrated that in repaired tetralogy patients a stiff right ventricle helped to prevent the right ventricle from dilating despite the volume loading effect of chronic pulmonary regurgitation, and the clinical impact of this was demonstrated by better exercise tolerance.[9]

Branch pulmonary artery stenosis or peripheral pulmonary stenoses will increase right ventricular afterload and increase pulmonary regurgitation.[8] It has recently been demonstrated that in most patients the majority of pulmonary regurgitation occurs from the left pulmonary artery.[10] In a study of 22 patients (3–16 years post-repair; transannular patch, n = 16; conduit, n = 2) undergoing pulmonary artery flow measurements by MRI, there was a mean (SD) pulmonary regurgitant fraction of 39 (10)% in the main pulmonary artery. The mean (SD) left pulmonary artery contribution to total regurgitant fraction was 54 (19)%, despite receiving 44 (13)% of forward flow. The left pulmonary artery contribution to total regurgitation was ⩾75% in four patients. The explanation for this preferential regurgitation from the left pulmonary artery is unclear, and is not related to the cross-sectional areas of the proximal branch pulmonary arteries. While the geometry of the main pulmonary artery bifurcation may have a role, a higher left pulmonary artery vascular impedance may be due to the smaller left lung whose volumes are further compromised by cardiomegaly predominantly occurring in the left chest.[w25] Previously reported restrictive lung defects in tetralogy of Fallot patients may also be caused by cardiomegaly.[11] [w26]

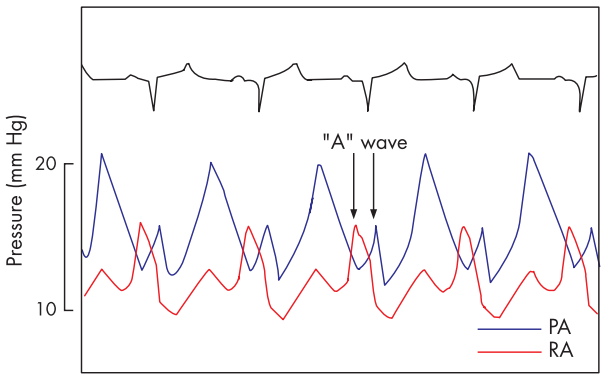

Figure 1 Simultaneous right atrial (RA) and pulmonary artery (PA) pressure in a patient with restrictive right ventricular physiology and an antegrade right atrial "A" wave transmitted into the pulmonary artery.

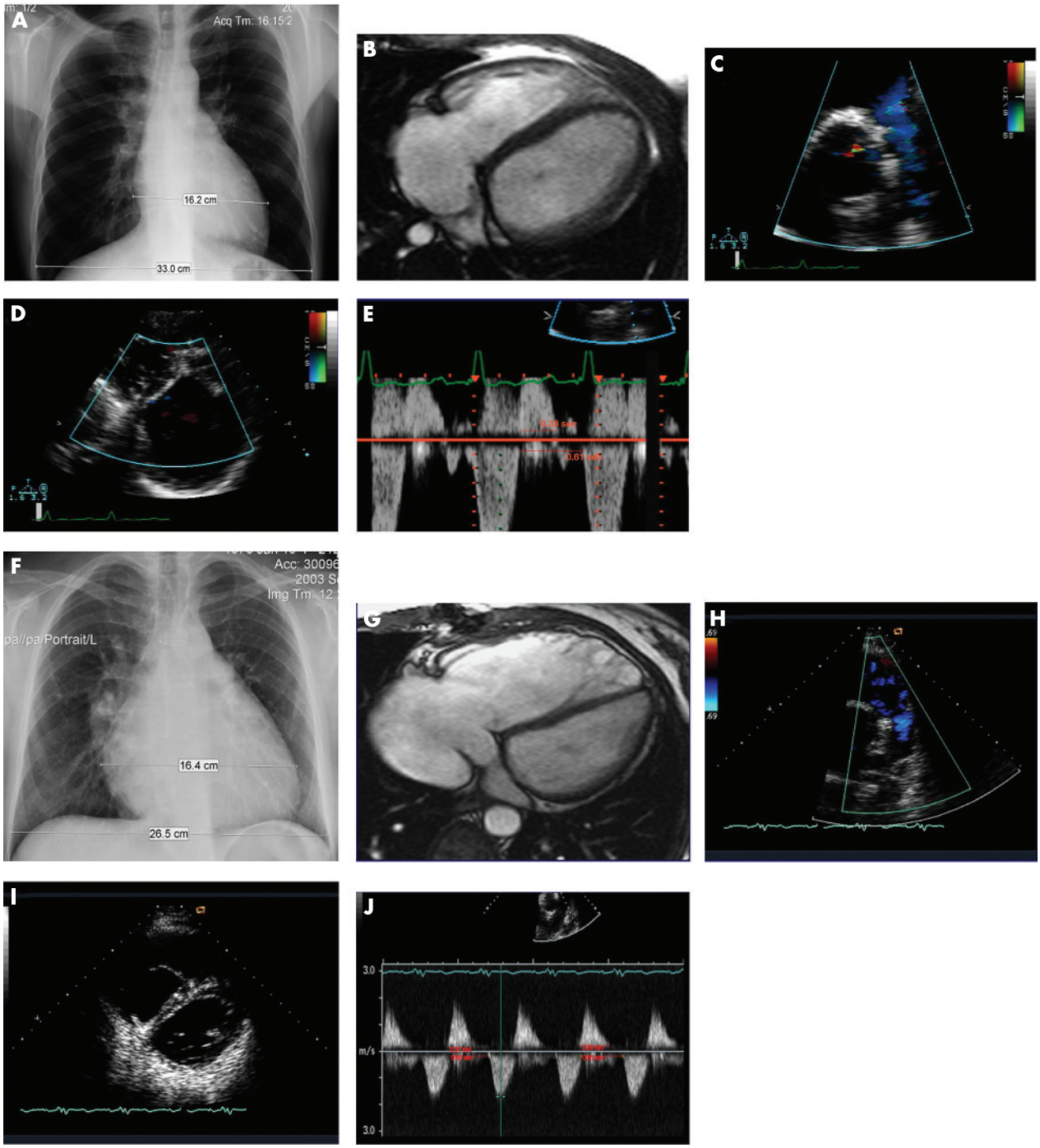

Figure 2 A comparison of two patients with repaired tetralogy of Fallot and pulmonary regurgitation. The patient in panels A–E has a restrictive right ventricle, with a small heart on a chest radiograph (A), small right ventricular volume by magnetic resonance imaging (MRI) (B), a non-obstructed right ventricular outflow tract (C), a small right ventricle seen in a short axis echocardiographic view (D), and Doppler evidence of restriction with an antegrade ''A'' wave in the pulmonary artery. The patient shown in panels F–J has a non-restrictive right ventricle, with a large heart on a chest radiograph (F), a dilated right ventricle by MRI (G), a non-obstructed right ventricular outflow tract (H), a large right ventricle in a short axis echocardiogram, and no ''A'' wave in the pulmonary artery Doppler spectrum. Despite the markedly different right ventricular responses, the pulmonary regurgitant indexes were similar.[w27]

Although pulmonary regurgitant fraction is often used in clinical MRI reports and published papers as an index of severity of regurgitation, this can be misleading. A small regurgitant volume in the presence of a small stroke volume can lead to a large regurgitant fraction. The real quantities of interest are the absolute regurgitant volume and the absolute right ventricular volumes (both indexed to surface area), as they reflect the true additional preload to the right ventricle.

Similarly, ratios of diastolic time intervals as suggested by Li can be misleading as an index of pulmonary regurgitation severity.[w27] For example, the patient with restrictive right ventricular physiology in fig 2 (panels A–E) has a ratio of pulmonary regurgitation duration to total diastole of 0.54, yet has a small right ventricular end-diastolic volume (61 ml/m^2) and small regurgitant fraction, whereas Li's index would predict that this patient would have a dilated right ventricle and severe regurgitation.

Right ventricular dilatation

Pulmonary regurgitation increases right ventricular preload and eventually leads to right ventricular dilatation. This is a slow insidious process and in congenital pulmonary regurgitation symptoms developed in 6% at 20 years and 20% by 40 years.[1] Indeed Ehrenhaft stated that his objections to transannular patches in the repair of Tetralogy arose from his experience of performing pulmonary valve replacements for congenital pulmonary regurgitation.[w7]

Many of the right ventricular effects of pulmonary regurgitation have been captured in a subacute porcine model of severe pulmonary regurgitation induced by stent deployment across the pulmonary valve.[12] Mean (SD) pulmonary regurgitant fraction was 49 (5.9)% at three months with right ventricular dilatation (right ventricular end-diastolic volume 160% of control) and left ventricular underfilling (left ventricular end-diastolic volume 86% of control) occurred in the pulmonary regurgitation group (fig 3). This was accompanied by an increase in the mass of the right ventricular free wall of 189% compared to control and a fall in right ventricular systolic function as measured by an end-systolic elastance that was only 85% of control at rest and 74% of control after a dobutamine challenge. Left ventricular systolic function was relatively well-preserved at 93% control at rest and 95% control after dobutamine.

The mechanoelectrical effect of pulmonary regurgitation on the right ventricle was examined in an ovine model[w28] in which two leaflets of the pulmonary valve were excised resulting in severe pulmonary regurgitation with a mean regurgitant fraction of 75 (10)% three months later. Monophasic action potentials measured by right ventricular epicardial suction electrodes (inlet, apex and outlet) demonstrated increased inhomogeneity of right ventricular activation by an increased variability of the time from the surface QRS to onset of the local monophasic action potential. Intracellular recordings in field-stimulated muscle found a 65% decrease in conduction velocity of volume-loaded muscle compared to controls, and this was attributed to an increase in intracellular resistivity. Both the increased inhomogeneity of activation and slowed conduction velocity in volume-loaded right ventricles are potentially proarrhythmic.

Davlouros assessed 85 adults 24.3 (7.5) years post-repair of tetralogy of Fallot by cardiac MRI.[13] Ninety per cent of these patients were in New York Heart Association (NYHA) functional class I or II, 56% had either a right ventricular outflow tract aneurysm or akinetic region, there was a wide distribution of pulmonary regurgitant fractions (0–55%, mean 24 (16)%), and right ventricular volumes (right ventricular end-diastolic volume 116 (34) ml/m^2, right ventricular end-systolic volume 56 (24) ml/m^2) were smaller than in the pulmonary valve replacement series reported below. Right ventricular dilatation was related to the severity of pulmonary regurgitation and the presence of an outflow tract aneurysm or akinetic region. Right ventricular mass was increased in the patients with tetralogy of Fallot and this correlated with the degree of right ventricular dilatation and the presence of peripheral pulmonary stenoses.

Left ventricular dysfunction

Left ventricular dysfunction is being increasingly recognised in symptomatic patients with tetralogy of Fallot, and indeed the presence of left ventricular disease may be a marker of the severity of the right ventricular disease. An important mechanism that compromises left ventricular filling is diastolic bowing of the interventricular septum into the left ventricular cavity that is already compromised by right ventricular dilatation within the pericardial space.

In Davlouros' MRI study left and right ventricular ejection fractions were correlated (correlation coefficient 0.67), suggest-

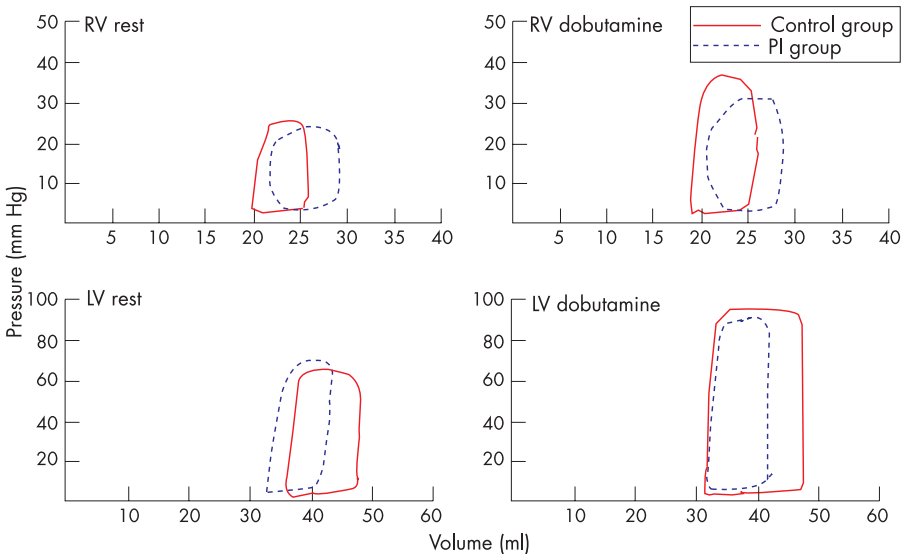

Figure 3 Right ventricular (RV) pressure–volume loops (upper panels) obtained in pigs subjected to pulmonary regurgitation by stent implantation (PI) in the right ventricular outflow tract. After three months of pulmonary regurgitation the right ventricular pressure–volume loop is shifted to the right to higher volumes, whereas the left ventricular (LV) pressure–volume loop is shifted to smaller volumes. Dobutamine increases stroke volume by 25% in the control animals, but in the pulmonary regurgitation animals stroke volume increases by 3% in the right ventricle and 9% in the left ventricle. Adapted from Kuehne *et al*.[12]

ing that right ventricular dysfunction can affect left ventricular performance.[13] Geva made stronger claims for the importance of left ventricular disease based on a study of 100 patients a median of 21 years after tetralogy of Fallot repair.[14] Eighty-eight per cent of the patients were in NYHA class I or II, and 12% in NYHA class III. Seventy-five per cent of the patients had had a right ventricular outflow patch, the remainder a conduit. Right ventricular volumes were higher in the patch repair group (median right ventricular end-diastolic volume 122 ml/m^2 in the patch group versus 106 ml/m^2 in the conduit group). Left ventricular ejection fraction was correlated with right ventricular ejection fraction (correlation coefficient 0.58). Longer QRS duration was associated with larger right ventricular volumes and mass and negatively correlated with right ventricular ejection fraction.

Logistic regression analysis of poor clinical state (NYHA class III) was attempted with two models, one including all variables and the other only considering right ventricle related variables. The fit of the models to the data as measured by the area under the receiver operating curve was comparable (almost 0.9). In the more parsimonious right ventricular variables model, right ventricular ejection fraction, right ventricular mass/volume ratio and older age at repair had the highest odds ratios. In the all variables model the highest odds ratios were left ventricular ejection fraction and age at repair, which led Geva to suggest that left ventricular factors were dominant causes of symptoms and exercise intolerance.[14] This may be an over interpretation of a more complex model that has no additional predictive value; however, some of the most symptomatic repaired tetralogy patients *do* have left ventricular dysfunction accompanying their severe right ventricular disease.

Incoordinate contractions may contribute to left ventricular dysfunction. Tetralogy of Fallot patients (n = 25, a median of 10 years post-repair) with right bundle branch block were found to have delayed time to peak strain in the septum as compared to the left ventricular lateral wall, as measured by tissue Doppler imaging.[w29] This right bundle branch block-induced left ventricular incoordination is different to the usual pattern seen in heart failure or dilated cardiomyopathy in which the left lateral wall lags behind the septum.[w30]

CLINICAL SEQUELAE OF PULMONARY REGURGITATION

Decrease in exercise tolerance

The majority of patients studied more than 10 years after repair have measurable exercise intolerance with group means typically being 80–90% predicted for normal individuals. Wessel examined the factors leading to a diminished exercise tolerance (males, 82 (21)% predicted; females 86 (29)% predicted) in a large group of patients (n = 123) at least one year after repair.[15] Poorer exercise capacity was related to cardiomegaly, right ventricular hypertension, pulmonary regurgitation, residual ventricular septal defect, pulmonary hypertension and arrhythmias. Subsequently, Wessel demonstrated a restrictive lung defect in repaired tetralogy patients that correlated with reduced exercise tolerance, with the diminished lung volumes related to cardiomegaly and pulmonary regurgitation.[w26]

Rowe studied 55 patients 15–37 years post-repair and found mean (SD) exercise duration was 92 (17)% of predicted and peak oxygen consumption was 31 (8) ml/kg/min (86 (18)% predicted).[11] Forty-five per cent of the patients had diminished vital capacity (<80% predicted). Pulmonary regurgitation was associated with increased right ventricular area and both of these were inversely related to exercise duration and vital capacity. Carvalho measured pulmonary regurgitation directly from pressure–volume loops constructed from biplane cineangiograms and found that patients with peak oxygen consumption <85% predicted had more pulmonary regurgitation.[w31] In patients assessed 10 (4.9) years post-repair, Norgard found a lower peak oxygen consumption and anaerobic threshold that was associated with low vital capacity and pulmonary regurgitation.[w32] Gatzoulis studied 41 patients 15–35 years post-repair and demonstrated the benefit of a stiff right ventricle in the presence of chronic pulmonary regurgitation.[9] All patients had pulmonary regurgitation and a lower peak oxygen consumption than controls, but those with Doppler evidence of right ventricular restrictive physiology had a smaller cardiothoracic ratio and higher peak oxygen consumption than those without restriction.

Finally, the effect of pulmonary regurgitation on left ventricular function has also been assessed.[16] Twenty-nine patients 16 (2) years post-repair of tetralogy had cardiac output and ventriculography measured during cycle ergometry. Although cardiac output increased appropriately, the increase in left ventricular ejection fraction was blunted; this depression in response was inversely correlated with right ventricular end-diastolic volume and the severity of pulmonary regurgitation, further emphasising how ventricular dilatation caused by pulmonary regurgitation may affect left ventricular performance.

Arrhythmias and sudden death

Pulmonary regurgitation and right ventricular dilatation are associated with ventricular tachycardia. Marie found that inducible ventricular tachycardia was more common in dilated right ventricles following tetralogy repair.[w33] Gatzoulis found that in a single surgeon series of 178 patients with a mean follow-up of 21 years, nine patients had documented ventricular tachycardia and four had died from sudden death.[17] Forty-one of these patients also had echocardiography performed, with 20 patients having restrictive right ventricular physiology as demonstrated by Doppler echocardiography. All patients with ventricular tachycardia or sudden death had QRS duration ≥180 ms. QRS duration correlated ($R^2 = 0.64$) with cardiothoracic ratio in the full group of patients. In the subset that had echocardiography, the mean (SD) QRS duration of the right ventricular diastolic restrictive physiology group was lower (129 (20) ms) than those with non-restrictive right ventricles (158 (13) ms).

In a subsequent multicentre study of 793 patients with mean follow-up of 21 years, 33 patients developed sustained ventricular tachycardia, 29 developed atrial flutter/fibrillation and 16 died suddenly (fig 4). Multivariate analysis demonstrated QRS duration ≥180 ms was strongly predictive of ventricular tachycardia (risk ratio (RR) 42), sudden death (RR 2.3) and atrial flutter/fibrillation (RR 3.4).[18] There were modest effects of a previous Waterston or Potts shunt on ventricular tachycardia (RR 1.1) and older age at time of repair on sudden death (RR 1.07). Atrial flutter/fibrillation was associated with

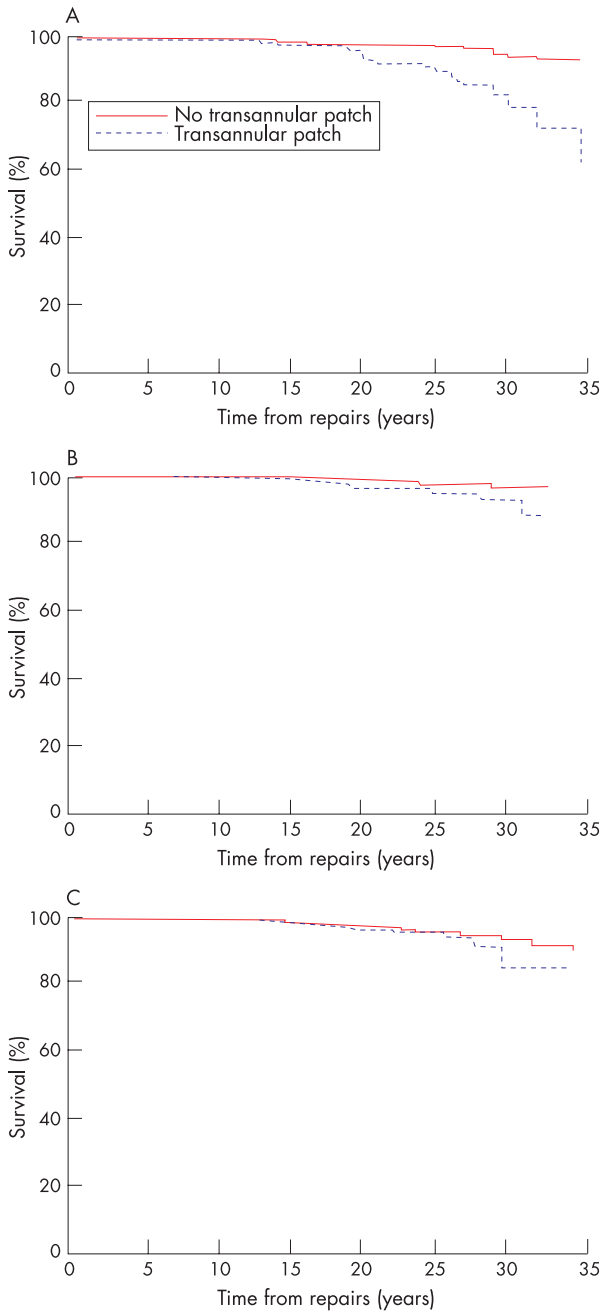

Figure 4 Tetralogy of Fallot patients repaired with a transannular patch have an increased risk of developing ventricular tachycardia (A), sudden death (B) and atrial arrhythmias (C). Adapted from Gatzoulis *et al*.[18]

previous Waterston/Potts shunt (RR 9.8), requirement for reintervention before 1985 (RR 3.5), QRS duration ⩾180 ms (RR 3.4), and older age at repair (RR 1.07).

It has been suggested that a transatrial–transpulmonary repair may lead to less right ventricular dysfunction and fewer arrhythmias due to avoidance of a right ventriculotomy. In a group of 71 patients with a transventricular repair (mean follow-up 9.7 years) and 36 with a transatrial–transpulmonary repair (mean follow-up 7.2 years), those that had undergone a transatrial–transpulmonary repair were more likely to be in NYHA class I, had fewer atrial arrhythmias, ventricular tachycardia and less severe pulmonary regurgitation.[w34]

Similar to the effects on exercise tolerance, tetralogy patients that have combined left and right ventricular dysfunction seem to be at increased risk of arrhythmias compared to those with just right ventricular problems. In a retrospective comparison of left ventricular function in tetralogy of Fallot patients with sudden cardiac death (n = 12) versus a randomly selected group of individuals with repaired tetralogy (n = 125), moderate or severe left ventricular dysfunction was found in 42% of the sudden death group compared to 6% of the control group.[19] Those patients with left ventricular systolic dysfunction also had significant right ventricular dysfunction with moderate to severe pulmonary regurgitation, that may have partially contributed to the left ventricular dysfunction by ventricular interdependence.

Survival

Cardiac deaths in repaired tetralogy are usually caused by either heart failure or sudden death. Hence survival is affected by similar factors such as exercise tolerance and arrhythmias.

Although Kirklin had shown that a transannular patch was a predictor of early postoperative death, several of the early tetralogy of Fallot series suggested that pulmonary regurgitation, or rather a transannular patch as a surrogate measure, had little impact on late survival.[w35] This discrepancy may have been due to too short a follow-up, inadequate means to quantify pulmonary regurgitation and right ventricular volumes, and death in the early postoperative period of the very patients with the most unfavourable anatomy.

The Mayo Clinic reported on late follow-up of a cohort of 163 patients operated on between 1955 and 1960, in whom there was a 20% hospital mortality.[20] There was an 86% 32 year actuarial survival in these survivors of the initial surgery compared to 96% survival in age and sex matched controls. They found that a transannular patch or previous Blalock–Taussig shunt did not affect survival. Independent predictors of worse survival were older age at operation and a higher ratio of right ventricular to left ventricular systolic pressure immediately postoperatively. It should be borne in mind that either of the latter two variables can be correlated with poor preoperative anatomy such as small pulmonary arteries. In addition the high postoperative mortality of the era would have led to the death of patients with predominantly the most unfavourable anatomy—for example, small pulmonary arteries, small right ventricular outflow tracts. Some of the patients that might be likely to have the most dramatic sequelae of a transannular patch did not survive to be included in the study.

More recent reports have demonstrated that pulmonary regurgitation can have considerable impact on long-term outcome. Nollert reported on 658 patients who underwent tetralogy repair from 1958 to 1977.[21] Operative deaths (n = 139, 21%) and deaths in the first postoperative year (n = 29, 4.5%) were excluded, resulting in a study group of 490 patients. Mortality started to increase at approximately 25 years postoperatively, and actuarial survival at 30 and 36 years was 89% and 85%, respectively. Cardiac deaths were due to sudden death (n = 13) or heart failure (n = 6).

Multivariate analysis showed important predictors of death were operation before 1970, preoperative polycythaemia and a

right ventricular outflow patch. Patients without a right ventricular outflow patch or preoperative cyanosis had a 36 year actuarial survival of 96%. Similarly, d'Udekem found a 86% survival at 30 years in 191 survivors of tetralogy repair.[22] Right ventricular patching, whether below the valve (18%) or across the valve (52%), was the most important predictor of poor outcome (cardiac death, right ventricular dilatation or NYHA class). Patients whose right ventriculotomy could be closed directly had smaller right ventricular/left ventricular end-diastolic dimensions and fewer had severe pulmonary regurgitation.

ASSESSMENT AND MANAGEMENT OF PULMONARY REGURGITATION

Patients with restrictive right ventricular physiology are protected from the volume loading effect of pulmonary regurgitation on the right ventricle. However, in the majority of patients with pulmonary regurgitation the volume load on the right ventricle results in progressive right ventricular dilatation. Surveillance should be directed at monitoring right ventricular dilatation and its sequelae, rather than pulmonary regurgitation per se. Clinical findings accompanying ventricular dilatation are decreased exercise tolerance and other signs and symptoms of heart failure. Evidence of right ventricular dilatation should be sought by chest radiography, echocardiography or MRI. It is important to obtain an estimate of right ventricular pressure—for example, from a tricuspid regurgitation jet by Doppler echocardiography. Evidence of elevated right ventricular pressure should initiate a search for right ventricular outflow tract obstruction or pulmonary artery stenoses. Since the pulmonary arteries are rarely adequately imaged in older children and adults this will usually necessitate a magnetic resonance scan.

Treating right ventricular outflow tract obstruction and branch pulmonary artery stenoses

Stenosis of a conduit of adequate diameter for the patient's body surface area has been treated by stenting the conduit, which can delay conduit replacement by several years.[w36 w37] In the future an increasing number of conduit stenoses will be treated by insertion of a pulmonary valve mounted on a stent. However, muscular right ventricular outflow tract obstruction (RVOTO) or development of a double chambered right ventricle will continue to require surgery. Branch pulmonary artery stenoses or peripheral pulmonary artery stenoses should be sought in all patients with pulmonary regurgitation as relieving these can decrease pulmonary regurgitation (fig 5).

Pulmonary valve replacement: surgical and transcatheter

Indications for pulmonary valve replacement include objective evidence of progressive right ventricular dilatation with symptoms of heart failure or documented arrhythmia. Davlouros provides a review of recent surgical pulmonary valve replacement series.[2]

Pulmonary valve replacement may lead to a reduction in right ventricular dilatation, improved exercise tolerance and decreased arrhythmias. There is considerable difficulty in comparing surgical series: patients may be referred for surgery at different stages in the disease process; there is considerable heterogeneity in the underlying anatomy; many patients have

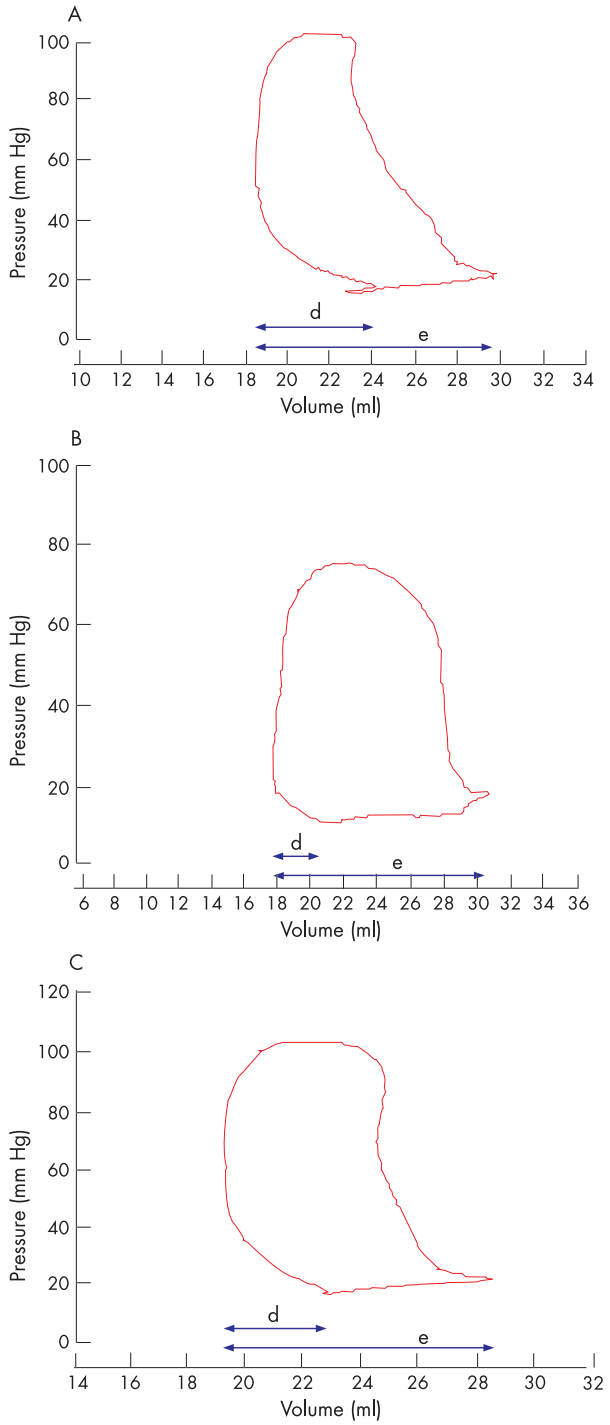

Figure 5 Stent insertion decreases pulmonary regurgitation in a patient with repaired tetralogy of Fallot with left pulmonary artery stenosis. In the baseline condition (A) pulmonary regurgitant fraction is 38%, and after stent deployment (B) pulmonary regurgitant fraction has decreased to 24%. Inflation of a balloon within the left pulmonary artery stent (C) results in an increase in pulmonary regurgitant fraction to 42%. The indentation in the bottom left hand corner of the right ventricular pressure–volume loops is caused by pulmonary regurgitation increasing right ventricular volume during "isovolumic" relaxation. Pulmonary regurgitant fraction is taken as the ratio d/e.

additional lesions that are addressed at the time of pulmonary valve replacement; and there are a wide range of valves or valved conduits that have been deployed in the pulmonary valve position. Furthermore, length of follow-up varies, and there are many techniques used to assess right ventricular function and volume in response to surgery. The current gold standard for right ventricular volume determination and quantitation of pulmonary regurgitation is MRI, but even with this technique right ventricular volume measurement is less accurate than left ventricular volume measurement, with errors typically in the range of 6–10%.[w38–40]

How dilated should the right ventricle be to consider pulmonary valve replacement? In a recent small series, right ventricles with end-diastolic volume >170 ml/m^2 did not recover following pulmonary valve replacement.[23] During the study period, 41 individuals with tetralogy of Fallot 34 (12) years post-repair underwent pulmonary valve replacement and 17 had adequate MRI to calculate ventricular volumes. A mean of 21 months after pulmonary valve replacement, right ventricular end-diastolic volume decreased to 66% of the initial value (163 (34) to 107 (26) ml/m^2). Reduction in right ventricular volumes did not occur in any ventricle with an initial end-diastolic volume >170 ml/m^2 or end-systolic volume >85 ml/m^2. Apart from the technical difficulties of measuring ventricular volumes in the presence of right ventricular trabeculations and establishing a normal range for right ventricles with aneurysmal dilatation of the right ventricular outflow tract, this is a small group of patients and more robust values from larger cohorts will be available in the future.

Large numbers of patients undergoing serial studies are required as there must be a time-dependent distribution of ventricular volumes before and following pulmonary valve replacement, and clinical interest resides in the conditional probability of achieving a certain smaller range of ventricular volumes given the current ventricular volumes. The complexity of the problem is demonstrated by one of the patients in Therrien's report whose right ventricle failed to recover despite a right ventricular end-diastolic volume of 148 ml/m^2. Preoperative ventricular dimensions alone may be an inadequate guide to reversibility of ventricular dilatation and arrhythmias following valve replacement.

Vliegen measured ventricular volumes and pulmonary regurgitant fraction 5.1 (3.4) months before and 7.4 (2.4) months after pulmonary valve replacement in 26 adults.[24] Right ventricular end-diastolic volume decreased by approximately 31% (166.8 (40.3) ml/m^2 to 114.3 (35.0) ml/m^2) and end-systolic volume also fell by 33% (99.0 (35.9) ml/m^2 to 66.3 (35.2) ml/m^2). Left ventricular volumes of the group as a whole were unaffected by pulmonary valve replacement. Group right ventricular ejection fraction was unaffected and remained at 42%, but when it was corrected for preoperative shunts and pulmonary regurgitation it increased from 25 (8)% to 43 (14)%. NYHA class improved following pulmonary valve replacement, for those initially in classes I and II. Those initially in classes higher than II did not improve.

Surgical repair can combine pulmonary valve insertion with reduction of aneurysmal right ventricular outflow tracts that act as large capacitance chambers,[w41] repair of proximal branch pulmonary artery stenoses, and intraoperative cryoablation. There is no consensus as to the optimal valve for pulmonary valve replacement, common choices being a xenograft or homograft. Eyskens measured the effect of pulmonary valve replacement on quantitative exercise tolerance pre- and 2.8 (1.4) years post-pulmonary valve replacement.[w41] There was an increase in ventilatory anaerobic threshold and slope of the oxygen consumption versus exercise intensity. There was no relationship between improvement in exercise tolerance and postoperative ventricular volumes; however, preoperative ventricular volumes were not measured.

Mechanical support for isolated right ventricular failure has been used in the immediate postoperative period, especially in cardiac transplant surgery, but there are no series as yet of right ventricular assist device insertion for chronic right ventricular failure.[w43 w44]

Transcatheter insertion of pulmonary valves

A variety of implantable pulmonary valves are being developed,[w45] but the Bonhoeffer valve is the most mature technology at present and is undergoing clinical trials.[3 w46–49] This consists of a bovine jugular venous valve sewn into a stent mounted on a balloon (18 mm, 20 mm or 22 mm) and delivered via a custom designed 20 French sheath.

The first reported case was of a 12-year-old boy with pulmonary atresia and ventricular septal defect in whom a pulmonary valve mounted on a stent was delivered into the 18 mm Carpentier-Edwards conduit.[w46] In the most recent report, 58 patients (median weight 56 kg, median age 16 years) with conduit stenosis or combined stenosis and regurgitation underwent successful percutaneous pulmonary valve replacement.[3] Right ventricular pressure fell (64 (17) to 50 (14) mmHg) and the right ventricular outflow tract gradient decreased (33 (25) to 20 (15) mmHg). Right ventricular end-diastolic volume decreased (94 (28) to 82 (24) ml/m^2) and left ventricular end-diastolic volume increased (64 (12) to 71 (13) ml/m^2). A sub-set of patients (n = 16) underwent maximal oxygen consumption measurements which showed a small increase following the procedure (26 (7) to 29 (6) ml/kg/min). Three patients had important complications requiring urgent surgery. In two the stent dislodged during delivery, and surgical stent retrieval and homograft replacement was performed. Predilatation of a calcified conduit led to conduit dissection and severe bleeding that required surgical exploration. The mean follow-up was 9.8 (1.4) months with no deaths.

The current recommendation is that implantation should be reserved for conduits/homografts of 16–22 mm diameter with a stenotic segment of ⩽5 cm.[w50] Techniques are being developed to allow percutaneous insertion of pulmonary valves into the dilated native right ventricular outflow tract by first reducing the diameter of the right ventricular outflow tract by a cuff and then delivering the valve into the cuff.[w51] The haemodynamic and clinical benefits of this approach have yet to be demonstrated.

Arrhythmia management

Routine Holter 24 h ECG monitoring in the absence of symptoms is rarely useful,[w52] but serial ECGs allow monitoring of QRS duration[17] and dispersion of QT and JT intervals.[w53] Prospective studies are required to evaluate the ability of signal averaged ECGs or micro-T wave alternans to predict clinical arrhythmia.

Inducible arrhythmias during invasive electrophysiological testing are difficult to interpret in the absence of documented clinically relevant tachycardia. Ventricular stimulation protocols are not standardised and vary widely in their aggressiveness. Particularly difficult to interpret is a polymorphic ventricular tachycardia evoked by an aggressive stimulation protocol. Khairy reported on a multicentre group of 252 patients with repaired tetralogy of Fallot, 37% as part of a routine screen and 63% with clinical symptoms or documented ventricular arrhythmias.[w54] Sustained monomorphic ventricular tachycardia was inducible in 30.2% and polymorphic ventricular tachycardia in 4.4%; these carried a relative risk of 5 and 12.9, respectively, of future clinical ventricular tachycardia or sudden cardiac death. Khairy's study is one of the few to provide a prognostic link between inducible polymorphic ventricular tachycardia and subsequent clinical events; however, due to the mixed entry criteria and variation in stimulation protocols, this a difficult study to interpret.

Documented atrial flutter or ventricular tachycardia should be followed by an invasive electrophysiological study to ablate atrial flutter, and at least to map if not ablate ventricular tachycardia. This is particularly the case if sustained ventricular tachycardia is documented in the absence of significant right ventricular dilatation—that is, in the absence of an explanatory mechanism. Endocardial ablation of ventricular tachycardia in tetralogy of Fallot can be challenging as the circuits are often deep and distant from the endocardium. Monomorphic ventricular tachycardias in these patients are often very sensitive to overdrive pacing, and many of these patients are candidates for combined pacemaker–defibrillators that can offer resynchronisation, overdrive pacing and defibrillation.

Resynchronisation therapy has also been suggested as a treatment for dilated right ventricles with right bundle branch block before the patients reach end-stage heart failure. In a report on seven patients with right ventricular dysfunction and right bundle branch block, atrioventricular pacing was performed at three different sites (apex, septum and outlet) and cardiac index and right ventricular dP/dtmax was found to increase as compared to atrial pacing.[w55]

Intraoperative electrophysiological mapping with cryoablation is a very useful addition to pulmonary valve replacement in patients with arrhythmias. Therrien reported on 70 patients undergoing pulmonary valve replacement, 15 (nine with ventricular tachycardia, six with atrial flutter) of whom had intraoperative mapping and/or cryoablation.[25] A striking finding was the 100% freedom from pre-existing atrial flutter/ventricular tachycardia at five years in patients who underwent intraoperative cryoablation at the time of pulmonary valve replacement, in comparison to the 68% freedom from arrhythmia in those who did not have intraoperative cryoablation. For the group as a whole there was no change in QRS duration at a mean of four years follow-up, while a control group of patients with tetralogy of Fallot showed a significant QRS prolongation over the same time period.

Van Huysduynen found that averaged QRS duration decreased from 151 (32) ms to 144 (29) ms early after pulmonary valve replacement (6–12 months) in 26 patients with repaired tetralogy of Fallot.[w56] The decrease in QRS duration correlated with the decrease in right ventricular end-diastolic volume measured by MRI. It is possible that the beneficial effects of pulmonary valve replacement on QRS duration in this report may be attributed to the short duration of follow-up, and the QRS may lengthen with time and recurrence of pulmonary regurgitation in the prosthesis.

Clearly there are many permutations of resynchronisation/overdrive pacing/defibrillators and/or intraoperative mapping/cryoablation and pulmonary valve replacement. Some form of antiarrhythmic therapy may still be required following pulmonary valve replacement. Increasingly therapeutic algorithms used in left ventricular disease such as β-blockers will be applied to right ventricular failure.

CONCLUSION

The deleterious effect of chronic pulmonary regurgitation is most clearly seen in the syndrome of exercise intolerance or arrhythmias associated with low pressure dilated right ventricles after repair of tetralogy of Fallot. During surgical repair these patients may have received a transannular patch, compounded by damage to the right ventricular outflow tract caused by a ventriculotomy, right ventricular patching, extensive muscle resection or damage to coronary branches. Although pulmonary regurgitation is a major mechanism, the right ventricular dilatation is often multifactorial in origin.

Compared to 30 years ago, more patients with tetralogy of Fallot with unfavourable anatomy (RVOTO, pulmonary arteries) are surviving and patients with combined right ventricular pressure and volume overload are increasingly being recognised. The management strategy has been one of first tackling obstructive lesions, and dealing with volume loading when dilatation is progressive. Homografts, valved conduits and xenograft valves all have finite lifespans and these patients will require multiple procedures during their lifetime. Percutaneous pulmonary valve insertion is a significant advance, but the long-term fate of the first generation valves remains to be determined. In addition, many patients also require resection of right ventricular outflow tract aneurysms or akinetic segments that can only be addressed by surgery. Despite improvement of haemodynamics following pulmonary valve replacement, many patients will still require antiarrhythmic therapy.

In addition to finding improved materials for valve replacement, the major challenge lies in timing an intervention on a dilating ventricle and the management of these patients during the periods of recurrent progressive volume overload in the intervals between procedures. Markers of the reversibility of ventricular dilatation remain elusive.

Additional references appear on the *Heart* website— http://heart.bmj.com/supplemental

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